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Sir:

Enclosed herewith please find a copy of U.S. Patent No.
4,192,877 and U.S. Patent No. 4,235,906 as cited in the
Information Statement recently filed on January 26, 1986.

Respectfully submitted,

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NN'-Alkanedioxydi[oxymethylene-(*N*-alkyltetrahydropaverinium)] dihalides (III).

R	m	n	X ⁻	M. p.*	Found (%)		Formula	Reqd. (%)	
					Hal	N		Hal	N
Me	2	0	Br ⁻	70—80°	16.0	3.0	C ₄₆ H ₆₂ Br ₂ N ₂ O ₁₂	15.7	2.75
Me	2	0	NO ₃ ⁻	50—55	—	5.76	C ₄₆ H ₆₂ N ₂ O ₁₈	—	5.70
Me	2	1	Br ⁻	85—95	15.3	2.7	C ₄₉ H ₆₄ Br ₂ N ₂ O ₁₂	15.5	2.7
Me	2	1	ClO ₄ ⁻	80—90	6.55	2.6	C ₄₉ H ₆₄ Cl ₂ N ₂ O ₂₀	6.6	2.6
Me	2	2	Br ⁻	93—103	15.8	2.7	C ₅₀ H ₆₆ Br ₂ N ₂ O ₁₂	15.3	2.7
Me	2	3	Br ⁻	70—80	14.5	2.65	C ₅₁ H ₆₈ Br ₂ N ₂ O ₁₂	15.1	2.6
Me	2	4	Br ⁻	90—100	14.6	2.85	C ₅₃ H ₇₀ Br ₂ N ₂ O ₁₂	14.9	2.6
Me	3	0	Br ⁻	140—148	14.75	2.7	C ₅₀ H ₆₆ Br ₂ N ₂ O ₁₂	15.3	2.7
Me	3	1	Br ⁻	85—95	15.0	2.6	C ₅₁ H ₆₈ Br ₂ N ₂ O ₁₂	15.1	2.6
Et	2	1	Br ⁻	50—60	15.8	2.7	C ₅₁ H ₆₈ Br ₂ N ₂ O ₁₂	15.1	2.6
Et	2	4	Br ⁻	65—75	15.0	2.7	C ₅₁ H ₇₁ Br ₂ N ₂ O ₁₂	14.5	2.5
Pr	2	1	Br ⁻	105—115	15.45	3.0	C ₅₃ H ₇₂ Br ₂ N ₂ O ₁₂	14.7	2.6

* With decomp. over a range.

(b) *Reaction of tetrahydropapaverine with a di-(ω -bromoalkyl) ester, and quaternisation of the product.* The oxalate (III; R = Me, $m = 3$, $n = 0$, X⁻ = Br). Tetrahydropapaverine was liberated from its hydriodide (171.6 g., *ca.* 0.36 mole) as in previous experiments and, after drying, the base was dissolved in anhydrous acetone (1 l.) and added to a solution of di-(3-bromopropyl) oxalate (60.6 g., *ca.* 0.18 mole) in anhydrous acetone (4 l.). Anhydrous potassium carbonate (54.65 g., 0.396 mole) was then added, and the mixture was boiled under reflux for 104 hr., with stirring and protection from moisture. The mixture was then allowed to cool, the inorganic solids were filtered off and rejected, and methyl bromide (140 g.) was passed into the cooled acetone filtrate under anhydrous conditions. The solution was then left at room temperature for 10 days, during which a gum was deposited. Anhydrous ether (4 l.) was then added, the mixture set aside, and the supernatant liquid was then decanted and rejected. The residue was then triturated with anhydrous ether; it solidified; the solid was filtered off, washed rapidly with anhydrous ether, and dried (165.6 g.). The product was then triturated with anhydrous acetone (550 ml.), the solvent decanted, and the residue triturated with anhydrous ether (550 ml.). After filtration, the residue was dried *in vacuo*, first at room temperature, then at 80—90°/0.5 mm. (45 hr.) and finally at 115—120°/1 mm. (45 hr.). Di-[3-(tetrahydro-*N*-methyl-2-papaverinyl)propyl] oxalate dibromide (132.5 g.) was obtained as a pale yellow solid, m. p. 140—143° (decomp.) (Found: C, 57.0; H, 6.4; Br, 15.2; Br⁻, 14.9; N, 2.9; O, 18.35. C₅₀H₆₆Br₂N₂O₁₂ requires C, 57.4; H, 6.4; Br, 15.3; N, 2.7; O, 18.3%).

The corresponding di-iodide (obtained by using methyl iodide in place of methyl bromide) was yellow and had m. p. 95—120° (decomp.) (Found: I, 22.7; N, 2.5. C₅₀H₆₆I₂N₂O₁₂ requires I, 22.3; N, 2.5%).

Unsymmetrical Monoesters (IV).—The intermediate ω -bromoalkanoic acids were prepared by the action of hydrobromic and sulphuric acid on the ethyl esters of the corresponding ω -hydroxy-acids.¹⁸

The salt (IV; R = R' = Me, $m = 5$, $n = 2$, X⁻ = I⁻). 6-Bromohexanoic acid (3 g., ~0.015 mole) and thionyl chloride (17.8 g.) were heated together under reflux for 3 hr., after which the excess of thionyl chloride was distilled off, finally with anhydrous benzene *in vacuo*. The yellow oily residue was then dissolved in anhydrous benzene (9 ml.); to this was gradually added 2-dimethylaminoethanol (1.38 g., ~0.015 mole) in anhydrous benzene, heat being evolved and crystals separating. The mixture was heated under reflux for 1 hr., cooled, and treated with an excess of anhydrous ether. The solid precipitate was filtered off, washed with ether, and dried *in vacuo* (4.3 g.); it was then dissolved in water (15 ml.), and the solution was made alkaline (pH 9) with 2*N*-sodium hydroxide. The resulting oil was extracted with chloroform, the extracts were washed with water and dried (MgSO₄), and the chloroform was then removed *in vacuo*. The residual crude dimethylaminoethyl 6-bromohexanoate was dissolved in ethyl methyl ketone (22 ml.) and treated with a solution of methyl iodide (3.15 g.) in ethyl methyl ketone (22 ml.). The mixture was left at room temperature for 95 hr., filtered to remove a trace of impurity, and treated with an excess of anhydrous ether. The precipitated solid (4.3 g.) was filtered off, washed with dry ether, and recrystallised from anhydrous ethanol-ether. 2-Dimethylaminoethyl 6-bromohexanoate methiodide was obtained as pale yellow crystals, m. p. 74—76° (Found: C, 33.95; H, 6.15; Hal, 46.45; N, 3.2. C₁₁H₂₃BrINO₂· $\frac{1}{2}$ C₂H₅·OH requires

¹⁸ Cf. Barger, Robinson, and Smith, *J.*, 1937, 718.

C, 33.9; H, 6.3; Hal, 46.8; N, 3.2%). This substance (1.78 g.) was dissolved in anhydrous acetone (10 ml.) and added to a solution of sodium iodide (0.61 g., 1 mol.) in anhydrous acetone (10 ml.). The resulting solution was heated under reflux for 1 hr., then cooled, and the inorganic solids were filtered off and rejected. Adding an excess of anhydrous ether to the filtrate precipitated a pale cream-coloured solid (1.56 g.). This was heated under reflux with laudanoline (3.5 g., 3 mol.) and anhydrous acetone (60 ml.) for 150 hr. The mixture was then cooled, and the supernatant liquid decanted from the gummy solid and rejected. The residue was washed by decantation with anhydrous acetone and triturated with anhydrous ether; the resulting cream-coloured solid (1.73 g. after drying *in vacuo*) was dissolved in chloroform and carefully precipitated with anhydrous ether. After two further precipitations, the product was dried (9 hr. at 50°/0.5 mm., 9 hr. at 80°/0.5 mm., and 9 hr. at 100°/0.5 mm.), giving *N*-(5,2'-dimethylaminoethyloxycarbonylpentyl)tetrahydropapaverine dimethiodide (1.21 g.) as cream-coloured crystals, m. p. 135–137° (decomp.) (Found: C, 46.7; H, 6.4; I, 31.5; N, 3.5; O, 12.3. $C_{32}H_{50}I_2N_2O_6$ requires C, 47.3; H, 6.2; I, 31.3; N, 3.45; O, 11.85%).

The valerate (IV; R = R' = Me, $m = 4$, $n = 3$, $X^- = I^-$). δ -Bromovaleric acid (2.8 g.) was converted into 3-dimethylaminopropyl δ -bromovalerate methiodide in a manner similar to that described in the previous experiment. Crystallised from ethanol-ether it was pale cream-coloured and had m. p. 57–58° (2.2 g.) (Found: C, 34.2; H, 6.3; Hal, 46.9; N, 2.7. $C_{11}H_{23}BrINO_2 \cdot \frac{1}{2}C_2H_5 \cdot OH$ requires C, 33.9; H, 6.3; Hal, 46.8; N, 3.2%). Treatment with sodium iodide and laudanoline as described above then yielded cream-coloured *N*-(4,3'-dimethylaminopropoxycarbonylbutyl)tetrahydropapaverine dimethiodide, m. p. 124–130° (decomp.) (from methanol-ether) (Found: I, 31.1; N, 3.25. $C_{30}H_{50}I_2N_2O_6$ requires I, 31.3; N, 3.45%).

Symmetrical Diamides (V).—Ethyleneimine¹⁹ with dicarboxylic acid chlorides gave¹² the following *NN'*-di-(2-chloroethyl)diamides: oxamide, needles, m. p. 204–205° (lit.,¹² 200°), from methanol (Found: C, 33.6; H, 5.2; Cl, 33.0; N, 13.1. Calc. for $C_4H_{10}Cl_2N_2O_2$: C, 33.8; H, 4.7; Cl, 33.3; N, 13.15%); succinamide, scales, m. p. 163–164°, from ethanol (Found: C, 40.35; H, 5.7; Cl, 29.05; N, 11.3. $C_6H_{14}Cl_2N_2O_2$ requires C, 39.8; H, 5.9; Cl, 29.5; N, 11.6%); glutaramide, plates, m. p. 146–147°, from acetone (Found: C, 42.1; H, 6.3; Cl, 27.7; N, 10.8. $C_6H_{16}Cl_2N_2O_2$ requires C, 42.35; H, 6.3; Cl, 27.8; N, 11.0%); adipamide, m. p. 154–155° (lit.,¹² 151°), used without crystallisation. When ethyleneimine was treated with carbonyl chloride the crude *NN'*-di-(2-chloroethyl)urea had m. p. 124.5–126° (lit.,¹² 127°) and was used without purification.

Treatment of these amides with sodium iodide in anhydrous acetone yielded the following *NN'*-di-(2-iodoethyl)diamides: oxamide, plates, m. p. 221–222° (decomp.), from aqueous dimethylformamide [Found: C, 20.8; H, 2.8; I, 58.55; N, 7.1. $2C_6H_{10}I_2N_2O_2 \cdot H \cdot CO \cdot N(CH_3)_2$ requires C, 20.8; H, 3.15; I, 58.7; N, 8.1%]; glutaramide, scales, m. p. 148–149°, from acetone (Found: C, 24.8; H, 3.7; N, 6.3. $C_6H_{16}I_2N_2O_2$ requires C, 24.7; H, 3.7; N, 6.4%); adipamide, prismatic needles, m. p. 166–167°, from acetone (Found: C, 26.9; H, 4.0; I, 56.1; N, 6.1. $C_{10}H_{18}I_2N_2O_2$ requires C, 26.55; H, 4.0; I, 56.2; N, 6.2%); *NN'*-di-(2-iodoethyl)urea, needles, m. p. 156–157°, from ethanol (Found: C, 16.7; H, 2.85; I, 68.8; N, 7.8. $C_5H_{10}I_2N_2O$ requires C, 16.3; H, 2.7; I, 69.0; N, 7.6%).

NN'-Oxalyl di-(*N*-2-aminoethyltetrahydropapaverine) Dimethiodide, (V; R = Me, $n = 0$, $X^- = I^-$).—A mixture of *NN'*-di-(2-iodoethyl)oxamide (0.66 g.), laudanoline (1.8 g.), and anhydrous benzene (40 ml.) was heated under reflux for 416 hr., then allowed to cool. The supernatant liquid was decanted and rejected, and the gummy residue washed by decantation three times with anhydrous benzene and dried *in vacuo*, then dissolved in methanol and precipitated with anhydrous ether. After repetition of this purification, the dimethiodide was obtained as a yellow solid (0.4 g.), m. p. 180–183° (decomp.) (Found: I, 22.1; N, 5.0. $C_{48}H_{84}I_2N_4O_{10}$ requires I, 22.9; N, 5.05%). Similar experiments with the glutaramide and adipamide gave as only solid product laudanoline hydriodide, m. p. and mixed m. p. 195–197°. However, the urea gave *NN'*-ureido di-(*N*-ethyltetrahydropapaverine) dimethiodide (IX), a yellow solid, m. p. 150–153° (decomp.) (from ethanol-ether) (Found: I, 22.8; N, 5.15. $C_{47}H_{84}I_2N_2O_6$ requires I, 23.5; N, 5.2%).

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¹⁹ Wystrach and Schaefer, *J. Amer. Chem. Soc.*, 1956, 78, 1263.